

## ORIGINAL ARTICLE

# Physicochemical stability assessment of all-in-one parenteral emulsion for neonates containing SMOFlipid

Maria Skouroliakou,<sup>1</sup> Aggeliki M Kountouri,<sup>1</sup> Sophia Hatziantoniou,<sup>2</sup> Katerina Koutri,<sup>3</sup> Antonia Chiou<sup>1</sup>

## ABSTRACT

The aim of the study was to assess the stability of all-in-one (AIO) parenteral admixture used for neonates, containing SMOFlipid, an alternative to soybean, an  $\alpha$ -tocopherol-enriched lipid emulsion. SMOFlipid, consisting of soybean oil, medium chain triglycerides, olive oil and fish oil, was introduced commercially in 2005. Stability assays consisted of the assessment of the admixture's macroscopic aspect, droplet size distribution, pH, peroxide value and  $\alpha$ -tocopherol concentration.

The admixture was stored at room temperature or at 4°C and analysed over time (0, 24 and 48 h). The SMOFlipid-containing AIO parenteral admixture was shown to be physicochemically stable. All changes were reversible, the droplet size was under the upper limit (0.5  $\mu$ m) set by the *US Pharmacopeia*, maximum loss for vitamin E was 25% and the lipid peroxidation occurred within 24 h after preparation. In conclusion, the addition of SMOFlipid to an AIO parenteral admixture for neonates did not affect its physicochemical stability, and it was safe for administration on the first day of its preparation.

## Introduction

Newborn low birth weight infants have very limited protein and energy reserves and so their duration of survival without a source of nutrition is approximately 7 days.<sup>1</sup> Early, aggressive nutritional support of neonates may establish positive nitrogen and energy balances to restore growth. In premature infants, immaturity of the respiratory system and gastrointestinal tract often precludes the use of parenteral feeding in the first days to weeks of life. Total parenteral nutrition (PN) is thus an essential component of nutritional support for neonates.<sup>1</sup>

PN consists of intravenously administering all nutrients—amino acids, glucose, lipids, electrolytes, vitamins and trace elements—needed by patients who cannot take normal alimentation.<sup>2</sup> Non-protein energy requirements come from two sources: carbohydrates and lipids. Carbohydrates are normally administered in the form of glucose because this is the form in which most dietary carbohydrates reach the body's tissues, while lipids are a high-caloric source of energy, reducing the incidence of hyperglycaemia and fatty liver associated with the use of glucose as the only calorie source.<sup>3</sup> In particular, lipids serve as a source of essential

fatty acids and long-chain polyunsaturated fatty acids (LC-PUFAs), which are very important for brain and retina development.<sup>4</sup> These nutrients can be administered separately or in one container (all-in-one (AIO) parenteral admixture), which has been shown to be clinically and economically advantageous. The benefits of an AIO admixture are limited by physicochemical stability, as the ingredients affect the stability of the final admixture.

The commercial intravenous lipid emulsions are oil-in-water emulsions containing neutral triglycerides derived from oil, such as soybean and safflower oil, egg yolk phospholipids as emulsifier and glycerine to adjust tonicity.<sup>5</sup> Until the 1980s, the lipid typically used in PN was soybean oil (alone or in combination with other oils rich in LC-PUFAs, such as safflower oil). In soybean oil the  $\omega$ -6 polyunsaturated fatty acid ((n-6) PUFA) linoleic acid comprises about 50% of fatty acids present.<sup>6</sup> Studies reported that administration of soybean oil in total PN could be associated with an increased production of peroxidative catabolites and therefore an aggravated risk of oxidative stress.<sup>7</sup> An approach to decrease the amount of linoleic acid and other n-6 PUFAs present in the emulsion has been to partly replace soybean oil with n-3 PUFAs, medium-chain triglycerides (MCTs) and monounsaturated fatty acids, using other oils such as olive oil, coconut oil and fish oil.<sup>8,9</sup> Emulsions containing mixtures of MCTs and long-chain triglycerides (LCTs) are preferable to pure LCT emulsions because it was found that the shorter hydrocarbon chains of MCTs present a stabilising effect on the emulsion.<sup>10</sup> Furthermore, a good balance of n-6/n-3 fatty acids in the phospholipid membrane is important because n-3 PUFAs, namely eicosapentaenoic and docosahexaenoic acids, produce eicosanoids that are less inflammatory and non-thrombogenic in comparison to those derived from n-6 arachidonic acid.<sup>12,13</sup> Recently an  $\alpha$ -tocopherol-enriched lipid emulsion (SMOFlipid, Fresenius Kabi, Bad Homburg, Germany), comprising all the above-mentioned benefits, has been proposed as an alternative to soybean oil, and appears to be well tolerated by humans when considering clinical and metabolic factors.<sup>7</sup>

The aim of this study was to assess the stability of AIO parenteral admixture for neonates containing SMOFlipid. Stability assessment of the admixture was based on the macroscopic aspect, droplet size distribution, pH, peroxide value and  $\alpha$ -tocopherol concentration.

<sup>1</sup>Department of Diabetics and Nutritional Science, Harokopio University, Athens, Greece

<sup>2</sup>Department of Pharmaceutical Technology, School of Pharmacy, University of Athens, Athens, Greece

<sup>3</sup>Dietetics Department, IASO Maternity Hospital, Athens, Greece

## Correspondence to

Dr Sophia Hatziantoniou, Department of Pharmaceutical Technology, School of Pharmacy, University of Athens, University Campus, Athens 15771, Greece; [shatzi@pharm.uoa.gr](mailto:shatzi@pharm.uoa.gr)

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## Method

### Preparation of PN admixture

When preparing a PN daily formula for neonates, numerous factors should be taken into consideration such as weight, age, clinical state of the neonate, environmental conditions—type of incubator, phototherapy, etc. In this study the AIO parenteral admixture was prepared for a 26-week-old boy. Table 1 shows the nutritional requirements for a neonate at gestational age <26 weeks. AIO parenteral admixtures for neonates were prepared at the IASO Maternity Hospital, Athens. The composition of AIO admixture (A) is shown in table 2. Admixtures (A1) without the addition of extra lipid-soluble vitamins (Vitalipid; Fresenius Kabi) were also prepared to serve as controls for the peroxide value test. The admixtures were placed into ethyl vinyl acetate plastic bags using an automated compounder (MicroMacro 12, Baxa, Englewood, Colorado, USA). To evaluate the affect of storage conditions, the AIO admixtures were stored separately, protected from light, at 4°C or 25°C for comparison. The stability of the admixtures over time was monitored by macroscopic aspect and measuring the droplet size distribution, pH, peroxide value and  $\alpha$ -tocopherol concentration immediately after preparation (0 h), at 24 and 48 h after preparation.

### Visual inspection

For visual inspection of AIO parenteral admixtures, the bag was inverted for sampling five times to re-disperse flocculation or sedimentation. An aliquot of the emulsion was placed in a beaker to observe its surface under normal light. The appearance of large colourless or yellow droplets at the surface indicates phase separation and unacceptable emulsion stability.

### pH Measurement

pH was monitored with a Metrohm 744 pH meter.

### Particle size measurements and physicochemical stability assessment

Droplet size distribution and physicochemical stability assessment were monitored according to methods I and II specified in chapter 729 of *US Pharmacopeia XXXI* (USP), 2009.<sup>14,15</sup>

**Table 2** Composition of all-in-one parenteral admixture (A)

Components	Volume (ml)	Quantity	kcal
Total volume	190.6		
Vamin Infant*	41.5		8.3
Glucose 50%	34.0		68.0
SMOFlipid*	14.0		28.0
NaCl 15%	0.2	0.512 mmol Na	
KCl 10%	1.8	2.412 mmol K	
Calcium gluconate 10%	9.4	2.068 mmol Ca	
MgSO <sub>4</sub> 25%	0.5	0.5 mmol Mg	
Natrium glycofosphate	1.5	3 mmol Na	
		1.5 mmol P	
Heparin	1.9	95 IU	
H <sub>2</sub> O for intravenous injection	76.2		
Soluvit*	2.6	0.806 mg thiamine 1.274 mg riboflavin 1.274 mg pyridoxine 0.0013 mg cyanocobalamin 0.104 mg folic acid 0.0156 mg biotin 10.4 mg nicotinamide	
Vitalipid ADD*	7.0	2310 IU retinol 140 IU vitamin D 7 IU $\alpha$ -tocopherol 105 $\mu$ g vitamin K <sub>1</sub>	

\*Fresenius Kabi, Bad Homburg, Germany.

Measurements were performed immediately after the preparation of the formulas and the influence of storage conditions was assessed keeping the samples separately at 25°C and 4°C. The physical stability of the formulas over time was assessed by monitoring the mean droplet size and the polydispersity index (PI) immediately after their preparation, 24 and 48 h later.

Photon correlation spectroscopy was used in compliance with method I to determine droplet size distribution expressed as mean droplet diameter and PI. The measurements were performed as follows:

**Table 1** Nutrition requirements for a neonate at gestational age  $\leq$ 26 weeks

	Day									
	1	2	3	4	5	6	7	8	9	10
Fluid (ml/kg)	100	115	130	145	160	160	160	160	160	160
Amino acids (g/kg)*	1.5	2.0	2.5	3.0	3.5	3.5	3.5	3.5	3.5	3.5
Dextrose (mg/kg/min)	6	7	8	9	10	11	2	13	14	14
Fat (g/kg)†	1.0	1.5	2.0	2.5	3.0	3.0	3.0	3.0	3.0	3.0
Calories (kcal/kg)	39	49	59	69	79	84	89	94	98	98
Protein	3.9	4.1	4.2	4.3	4.4	4.2	3.9	3.7	3.6	3.6
Sodium (mEq/kg)	–	–	1	2	3	3	3	3	3	3
Potassium (mEq/kg)	–	2	2	2	2	2	2	2	2	2
Calcium (mg/kg)	30	40	50	60	70	70	70	70	75	75
Phosphorus (mg/kg)	–	20	30	40	45	45	50	50	55	55
Magnesium (mg/kg)	–	5.5	7	8	8.5	9	10	10	10.5	10.5
Soluvit (ml)‡	–	–	–	–	2.2	2.2	2.2	2.2	2.2	2.2
Vitalipid Adult (ml)§	–	–	–	–	5	5	5	5	5	5
Vitamin preparation										
Brand name	Concentration	Vitamin A	Vitamin D	Vitamin E	Vitamin K					
Vitalipid adult	Per 10 ml	3300 IU/990 $\mu$ g	200 IU/5 $\mu$ g	10 IU/9.1 mg	150 $\mu$ g					
Vitalipid infant	Per 10 ml	2300 IU/690 $\mu$ g	400 IU/10 $\mu$ g	7.0 IU/6.4 mg	200 $\mu$ g					

\*Vitamin Infant (Fresenius Kabi, Bad Homburg, Germany) is used as a source of amino acids.

†SMOFlipid (Fresenius Kabi) is used as a source of fat. SMOFlipid is administered separately by a syringe pump.

‡Fresenius Kabi.

§To provide adequate quantities of lipid-soluble vitamins, Vitalipid Adult (Fresenius Kabi) is used instead of Vitalipid Infant.

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50 µl of the dispersion was diluted in high-performance liquid chromatography (HPLC)-grade water (pH 5.6–5.7) to 3 ml final volume, and z-average mean was measured. Samples were scattered (633 nm) at an angle of 90° and measurements were made at 25°C in a photon correlation spectrometer (Zetasizer 3000HS<sub>v</sub>, Malvern Instruments, Malvern, UK) and analysed using the CONTIN method (Malvern Software).

For the large-diameter tail assessment, laser diffraction was used for method II using Mastersizer S (Malvern Instruments) fitted with a small volume sampler set at 50% of its speed capacity. The focal lens was 330 mm having size range 0.5–880 µm. The stirrer was filled with water double-filtered through 220 nm filters and the background was measured. Aliquots of the samples were added to the stirrer until obscuration was achieved at about 20%. Each sample was measured in triplicate, setting 2000 scans/run. The real refractive index (RI) was set at 1.456 and the imaginary RI at 0.01.

### Peroxide value

Peroxide concentration (µmol thiobarbituric (tert-butyl hydroperoxide or TBH) equivalent/litre) of admixture A over time was measured spectrophotometrically by the ferrous oxidation of xylenol assay.<sup>16</sup> This method is based on the fact that hydroperoxides formed from lipid peroxidation, oxidise ferrous and the resulting ferric iron binds to xylenol orange to produce a coloured complex that is detected at 560 nm. Admixture A1 had the same compositions as admixture A, but did not include Vitalipid. The vitamin-free lipid admixture A1 served as a control to test the influence of α-tocopherol content on the sensitivity of the admixture to peroxidation. TBH served as a reference.

### Vitamin E determination

Vitamin E determination was done according to Skouroliakou *et al.*<sup>17</sup> An aliquot (5 ml) of the admixture was transferred into a glass tube. Subsequently, sodium chloride (1 g) and ethanol (1 ml) were added and vortex mixed, followed by extraction with chloroform (4 × 3 ml) containing butylated hydroxytoluene (100 µg/ml). The organic layers were combined, dried over sodium sulphate (Na<sub>2</sub>SO<sub>4</sub>, 0.5 g), and evaporated under a stream of nitrogen. The residue was dissolved in chloroform/isopropanol 3:1 (1 ml) and subjected to HPLC analysis. All experiments were performed in triplicate under light protection. Samples were kept at -4°C in dark glass vials until analysis. HPLC analysis was carried out on an Agilent Technologies (formerly Hewlett-Packard (HP), Avontale, Pennsylvania, USA) series HP 1050 system equipped with an autosampler and an HP1046A fluorescence detector connected to an HP integrator and an HP Chemstation. A Nucleosil 120-5 C18 column (Macherey-Nagel, Düren, Germany) was used. Reverse-phase HPLC, resulting in detection of tocopherols was performed as previously described by using a quaternary solvent system consisting of water (acidified with phosphoric acid at pH 3), methanol, acetonitrile and isopropanol, with gradient elution on the column and fluorescence detection.<sup>18</sup> The excitation wavelength was set at 295 nm and the emission wavelength at 330 nm. Injections of 50 µl were performed. Tocopherol concentration was calculated by the chromatographic peak area under curve of the sample and a calibration curve.

### Data analysis

Data are presented as mean±SD. Comparisons between different time and temperature points were performed using the non-parametric Friedman test for ranked values. p Values <0.5 were considered statistically significant. All analyses were performed using SPSS V.12.0 statistical software.

## Results

### Visual inspection

Visual examination for emulsion status was performed by using the criteria of creaming, flocculation and coalescence. The presence of a

cream layer—a dense white layer at the top of the admixture—was visible in admixture A after 24 h stored at 25°C or 4°C. In all cases, the boundary between phases was well defined, and redispersibility of the cream layer occurred after five gentle inversions. Discolouration of the cream layer, oil globules or yellow traces were not observed in admixture A, indicating that coalescence did not occur.

### pH Study

The pH value of the mixtures was 6.03±0.09, without statistically significant changes at different times and temperatures.

### Droplet size distribution

On the preparation day the droplets of the dispersed phase were measured giving a mean hydrodynamic diameter of 348.0±9.5 nm and a good homogeneity, as shown from the PI value (table 3). The large-diameter tail assessment showed that 100% of the droplets had diameters less than 1.24 µm.

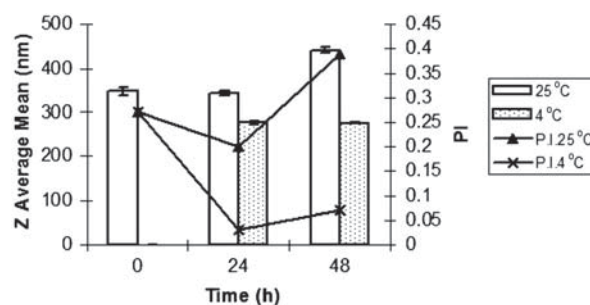
Storage at 25°C did not significantly alter the physicochemical characteristics of the dispersed phase for the first 24 h. However, at 48 h of storage at room temperature a group of dispersed droplets between 35.6 and 103.6 µm in size appeared, having a weight percentage greater than 5 µm of 1%, setting the sample above the acceptable upper limit of 0.05%. Storage at 4°C seems to improve the dispersion, giving smaller particles and low PI values and indicating excellent homogeneity (table 3). The dispersed droplets retain their characteristics for at least 48 h of storage at 4°C (figure 1).

### Peroxide value

The peroxide concentration in admixtures A and A1 stored at 25°C or 4°C over time are given in table 4. The results are expressed as µmol TBH equivalent/litre. Lipid peroxidation occurred within 24 h after preparation. The peroxide concentration ranged from 19.47±0.21 to 30.69±0.78 µM and was influenced by storage conditions and time. In A and A1 admixtures there was a statistically significant increase in peroxide concentration over time (p=0.001) and at 25°C (p=0.002). The lipid peroxide concentration in admixture A was significantly lower than in admixture A1; A versus A1, p=0.013.

**Table 3** Average size and polydispersity index (PI) of the formulation at different storage conditions over time

Time (h)	4°C		25°C	
	Size±SD (nm)	PI	Size±SD (nm)	PI
0	348.0±9.5	0.27	348.0±9.5	0.27
24	276.3±5.0	0.03	343.3±5.6	0.20
48	275.3±1.7	0.07	441.9±6.1	0.39



**Figure 1** Influence of storage conditions on the distribution characteristics of the formulations' dispersed droplets. PI, polydispersity index.

**Table 4** Peroxidation study of admixture at different storage conditions over time. Peroxide values expressed as thiobarbituric (tert-butyl hydroperoxide) equivalent concentration ( $\mu\text{M}$ )

Time (h)	A		A1*	
	4°C	25°C	4°C	25°C
0	19.47±0.21	19.47±0.21	21.80±0.59	21.80±0.59
24	26.75±0.77	27.11±0.24	28.22±0.51	29.07±1.11
48	28.12±0.24	27.76±0.86	28.59±0.30	29.11±1.15

\*A1, all-in-one admixture without lipid-soluble vitamins.

### Vitamin E determination

Determination of  $\alpha$ -tocopherol was performed after liquid-liquid extraction of the admixtures. The concentration of  $\alpha$ -tocopherol immediately after preparation was found to be  $33.74\pm 4.30$   $\mu\text{g/ml}$ .  $\alpha$ -Tocopherol proved to be relatively stable under the conditions tested. The highest loss determined was approximately 20% of the initial vitamin E concentration (table 5). The presence of other tocopherol vitamers ( $\delta$ -tocopherol,  $\gamma$ -tocopherol or  $\beta$ -tocopherol) was also detected in all samples. This can be attributed to the tocopherol naturally occurring in soybean, olive and fish oils that are contained in SMOFlipid, apart from Vitalipid contained in the admixture. The content of the other tocopherols was not drastically altered over time in the PN admixtures (data not shown).

### Discussion

Intravenous lipids are critical components of PN admixtures by providing essential fatty acids and dense calories. The majority of PN admixtures for neonates and adults are composed of plant-based lipids, primarily soybean oil.<sup>19</sup> Recently, the view has developed that the use of lipid emulsions based entirely on soybean oil may not be optimal or may even be harmful due to their high content of linoleic acid, a pro-inflammatory, immunosuppressive and pro-coagulatory lipid.<sup>12</sup>

In neonates, and particularly in premature infants with compromised lung function, a reduction in the amounts of potentially pro-inflammatory n-6 fatty acids from soybean oil may be indicated given their influence on pulmonary vasculature.<sup>20</sup>

The use of other oils, such as olive oil, coconut-derived oil or fish oil in lipid emulsions, which have specific anti-inflammatory effects due to their elevated content of n-3 fatty acids, might offer additional clinical benefits.<sup>9</sup>

Emulsions are inherently unstable dispersion systems, and even slight changes in their composition or storage conditions may result in droplet aggregation, coalescence or even phase separation (creaming).<sup>21</sup> In this study, changes (creaming) that were observed by visual examination were all reversible.

Instability of a PN admixture begins with droplet coalescence leading to the formation of large-diameter fat globules that are potentially embolic upon intravenous infusion. The particle diameters must be in the range of 0.4–1  $\mu\text{m}$  to mimic the size of chylomicrons.

**Table 5**  $\alpha$ -Tocopherol concentration of admixture A at different storage conditions over time

Time (h)	4°C		25°C	
	$\alpha$ -Tocopherol ( $\mu\text{g/ml}$ )	% Retention*	$\alpha$ -Tocopherol ( $\mu\text{g/ml}$ )	% Retention*
0	33.74±4.30	100	33.74±4.30	100
24	27.67±3.74	83	31.95±2.43	95
48	26.69±2.57	80	27.04±3.90	81

\*% Retention was calculated as the ratio of  $\alpha$ -tocopherol concentration at a certain time period to the initial concentration (immediately after preparation)×100.

Larger droplets (5–10  $\mu\text{m}$ ) are likely to be trapped in the capillaries and the lungs. Particle size measurements and physicochemical stability assessment according to methods I and II in chapter 729 of USP showed that the physicochemical characteristics of the AIO admixtures were influenced by time and storage conditions.<sup>14,15</sup> The droplets of the dispersed phase were within the specifications and were maintained for 24 h at 25°C. A group of dispersed droplets 5–1  $\mu\text{m}$  was detected after 48 h, indicating the beginning of phase separation. Storage at 4°C seems to improve the dispersion, giving smaller particles and low PI values and indicating excellent homogeneity, which was maintained unaltered for at least 48 h (table 3). Previous studies have found that the physicochemical properties and the stability of AIO admixtures are greatly influenced by the origin of the lipids used.<sup>11</sup>

In general, paediatric parenteral admixtures are more acidic than those for adults because they have a higher content of taurine and branched-chain amino acids.<sup>17</sup> The optimum pH of the AIO parenteral emulsion ranges from 6 to 7.<sup>22</sup> This pH range allows ionisation of the phosphate groups at the surface of the lecithin film, leading to an optimum surface charge for the droplets that protects lecithin from hydrolysis and favours emulsion stability. pH values lower than 5.0 result in increased droplet size and coalescence. The AIO admixtures in this study had pH values of about 6 and were stable over time. In a previous study, the pH value of an AIO admixture containing Intralipid (Fresenius Kabi, Uppsala, Sweden) was found to be around 5.83, and was reduced to 5.05 after 48 h.<sup>17</sup> The difference in pH stability of the AIO admixtures in this study could be attributed to the different lipid emulsion used. Intralipid is a soybean oil-based emulsion, while SMOFlipid is an emulsion of different lipids.

The use of a lipid emulsion based on MCTs, fish, olive and soybean oil lipid emulsion instead of a soybean oil-based emulsion seems to affect the lipid oxidation of the parenteral emulsion.<sup>17</sup> The prepared AIO admixtures showed increased resistance to lipid peroxidation that was found to be dependent on time and storage conditions (table 4). This result could be attributed to two factors: the presence of vitamin E which acts as an antioxidant preventing lipid peroxidation, and the presence of n-3 PUFAs and MCTs, which are less vulnerable to oxidation than n-6 PUFAs.<sup>11,17</sup>

Lipid emulsions containing MCTs may, to some extent, protect LC-PUFAs from  $\beta$  oxidation.<sup>23</sup> In addition, the provision of alternative emulsions containing oil mixtures which are less inflammatory, such as those rich in n-9 fatty acids, may be better for redox status.<sup>24</sup> Our results are in accordance to Pironi *et al*,<sup>25</sup> who studied the peroxidation potential of fat emulsions in AIO admixtures.

The necessity of fat-soluble vitamin supplementation in preterm neonates was documented many years ago.<sup>26</sup> Preterm infants are most likely to develop deficiencies in vitamins due to inadequate body stores. It is also well known that oxidative stress is related to morbidities associated with prematurity and that vitamin E can be used as an antioxidant defence of the body.<sup>27</sup> Vitamin E is a major free radical scavenger. Tocopherols inhibit lipid peroxidation by scavenging lipid peroxy radicals much faster than the radicals can react with the fatty acid side chains, thus breaking the chain reaction.<sup>28</sup> Vitamins are commonly believed to be among the least stable ingredients in PN admixtures and thus it is recommended that they should be added immediately before infusion or that infusion should be commenced within 24–48 h after addition.<sup>29</sup> The stability of vitamins may be affected by several factors, such as pH, light exposure, temperature and storage time.<sup>30</sup>

In this study, the vitamin E concentration was found to be time and storage dependent. Administration at room temperature immediately after preparation up to 24 h means that about 90% of the vitamin E content will reach the patient. Storage at 4°C

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seems to affect vitamin E stability 24 h after preparation, while the maximum loss reaches 20% 48 h after preparation under both storage conditions (table 5).

### Conclusions

Our results demonstrate that within therapeutic demands, AIO mixtures containing SMOFlipid are suitable for neonates as they proved to be physically stable for 2 days and relatively chemically stable for 24 h. In these admixtures, almost 90% of the nominal amounts of vitamin E will reach the patient, while the droplet size dispersion is within the limits set by USP, indicating that these AIO admixtures are stable for at least 24 h and making their administration safe during this time period. The peroxide load did not increase significantly, indicating that the use of lipids containing n-3 fatty acids and MCTs are safer than those containing solely n-6 fatty acids. Although the results appear promising, future studies in paediatric patients are needed to support the safety and efficacy of these novel parenteral emulsions in this age group.

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## Physicochemical stability assessment of all-in-one parenteral emulsion for neonates containing SMOFlipid

Maria Skouroliakou, Aggeliki M Kountouri, Sophia Hatziantoniou, Katerina Koutri and Antonia Chiou

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